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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/055,842	01/23/2002	Nicholas W. Gale	REG 900A	7875

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EXAMINER
JONES, DAMERON LEVEST

ART UNIT	PAPER NUMBER
1616	10

DATE MAILED: 09/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application N .	Applicant(s)	
	10/055,842	GALE ET AL.	
	Examiner	Art Unit	
	D. L. Jones	1616	

-- The MAILING DATE of this communication appears n the c ver sheet with the correspondenc address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-46,49,52-59 and 62* is/are rejected.

7)☒ Claim(s) *47,48,50,51,60,61,63 and 64* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

ACKNOWLEDGMENTS

1. The Examiner acknowledges receipt of Paper No. 8, filed 6/19/03, wherein claims 1-42 were canceled and claims 43-64 were added.

Note: Claims 43-64 are pending.

RESPONSE TO APPLICANT'S ARGUMENTS/AMENDMENT

2. The Applicant's arguments filed 6/19/03 (Paper No. 8) to the rejection of claims 1-4 and 11-42 made by the Examiner under 35 USC 103 and/or 112 have been fully considered and deemed persuasive for the reasons set forth below.

112 Second Paragraph Rejection

The previously pending 112 rejection is WITHDRAWN because Applicant has canceled the original claims.

103 Rejection

The previously pending 103 rejection is WITHDRAWN because Applicant has canceled all of the original claims. However, it should be noted that the prior art rejections read on the newly added claims as set forth below.

Note: It is duly noted that Applicant asserts that additional limitation (e.g., the imaging agent is a radionuclide or chelate has been incorporated into the new claims and thus, not obvious by the prior art. However, the cited prior art, Anderson et al, would render both a chelate and/or imaging agent obvious as set forth in the 103 rejection below.

NEW GROUNDS OF REJECTION

112 First Paragraph Rejection

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 43, 46, 49, 57-59, and 62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an ephrin B2 nucleic acid or polypeptide, does not reasonably provide enablement for all molecules that detect ephrin B2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are several guidelines when determining if the specification of an application allows the skilled artisan to practice the invention without undue experimentation. The factors to be considered in determining what constitutes undue experimentation were affirmed by the court in *In re Wands* (8 USPQ2d 1400 (CAFC 1986)). These factors are (1) nature of the invention; (2) state of the prior art; (3) level of one of ordinary skill in the art; (4) level of predictability in the art; (5) amount of direction and guidance provided by the inventor; (6) existence of working examples; (7) breadth of claims; and (8) quantity of experimentation needed to make or use the invention based on the content of the disclosure.

(1) Nature of the invention

Th1e claims are methods and uses thereof comprising a molecule that detects ephrin B2 coupled to an agent. The agent may be a radionuclide, chelate, carboplatin, cisplatin, vincristine, methotrexate, paclitaxel, docetaxel, 5-fluorouracil, UFT, hydroxyurea, gemcitabine, vinorelbine, irinotecan, tirapazamine, matrilysin, gelonin, ricin A, ricin B, saporin, bryodin 1, bryodin 2, momordin, pokeweed antiviral protein from seeds, trichokirin, or abrin.

(2) State of the prior art

The references do not indicate which specific all possible ephrin B2 molecules or the all possible classes of ephrin B2 molecules which are useful with the claimed invention. Likewise, the prior art does not indicate all possible ephrin B2 molecules which are useful with the instant invention (see, for example, Anderson et al, US Patent No. 2002/0136726 A1).

(3) Level of one of ordinary skill in the art

The level of one of ordinary skill in the art is high. Claims 43, 46, 49, 57-59, and 62 encompass a vast number of possible ephrin B2 binding molecules. Applicant's specification does not enable the public to make or use such a vast number of possible molecules to be used in combination with the agents above.

(4) Level of predictability in the art

The art pertaining to the ephrin B2 binding molecules is highly unpredictable. Determining the various types of molecules or class of molecules that will bind to ephrin B2 requires various experimental procedures and without guidance that is applicable to

all ephrin B2 binding molecules, there would be little predictability in performing the claimed invention.

(5) Amount of direction and guidance provided by the inventor

Claims 43, 46, 49, 57-59, and 62 encompass a vast number of ephrin B2 binding molecules. Applicant's limited guidance does not enable the public to prepare such a numerous amount of ephrin B2 binding molecules in combination with various agents. There is no directional guidance for the molecules that will binding ephrin B2 and be coupled to an agent that will yield the same or similar results as wherein the ephrin B2 molecule is an ephrin B2 binding nucleic acid or polypeptide, especially, since, Anderson et al disclose that it is known for *specific* ephrin B2 molecules to be conjugated to an agent for analyzing the stages of angiogenesis. Hence, there is no enablement for all possible permutations and combinations of the ephrin B2 binding molecules which are conjugated to an agent.

(6) Existence of working examples

Claims 43, 46, 57-59, and 62 encompass a vast number of molecules. Applicant's limited working examples do not enable the public to prepare such a numerous amount of molecules-agent combinations. While Applicant's claims encompass a plethora of possible molecules which may bind ephrin B2, the specification provides focuses on ephrin B2 binding nucleic acids and polypeptides.

(7) Breadth of claims

The claims are extremely broad due to the vast number of ephrin B2 molecules known to exist.

(8) Quantity of experimentation needed to make or use the invention based on the content of the disclosure

The specification does not enable any person skilled in the art to which it pertains to make or use the invention commensurate in scope with the claims. In particular, the specification failed to enable the skilled artisan to practice the invention without undue experimentation. Furthermore, based on the unpredictable nature of the invention, the sate of the prior art, and the extreme breadth of the claims, one skilled in the art could not perform the claimed invention without undue experimentation.

103 Rejection

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 43-45, 49, and 52-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (US 2002/0136726 A1).

Anderson et al disclose artery smooth muscle and vein smooth muscle specific proteins and their uses which involve the use of a transmembrane ligand, ephrin-B2 (see entire document, especially, abstract). In addition, Anderson et al disclose (a) once embodiment involves an oligonucleotide encoding a targeting molecule wherein the targeting molecule is composed of a nucleic acid which encodes a promoter and/or enhancer region and a second nucleic acid which encodes a polypeptide targeted to the

arteries. The targeting molecules may be administered to a mammal to modulate (e.g., inhibiting) angiogenesis (page 2, paragraph [0011]; page 8, paragraph [0060] – [0061]; page 8, paragraph [0063]). (b) Another embodiment relates to a method of modulating angiogenesis (e.g., inhibiting or promoting) or inhibiting tumor growth in a mammal (page 22, paragraph [0013]; page 13, paragraph [0092]). (c) The terms ephrin and Eph refer to ligands and receptors, respectively that can be used from any animals (e.g., mammals/non-mammals, vertebrates/non-vertebrates, including humans) (page 4, paragraph [0027]). (d) Another embodiment involves testing an effect of an agent (e.g., a drug, a nucleic acid, a gene product, or a targeting molecule) on growth, development, recruitment, and/or proliferation of arties. The method may be administered to a subject having a tumor (page 5, paragraph [0043]; page 7, paragraph [0056]). (e) Possible screening approaches include screening for angiogenic effects, anti-angiogenic effects, anti-thrombotic effects, anti-stenotic and/or anti-restenotic effects, inhibition of formation of atherosclerotic plaques, and effects of vasotension (page 8, paragraph [0063]; pages 8-9, paragraph [0065]). (f) The ephrin compositions may comprise a label which may be a radioactive isotope, a fluorescent label, a colorimetric label, an enzyme label, an affinity label, and epitope label, and a chemiluminescent label (page 9, paragraph [0068]). (g) The targeting agents may be an imaging agent (page 10, paragraph [0077]; page 11, paragraph [0079]). (h) Targeting vehicles may be administered using parenteral, oral, transdermal, topical or rectal administration (page 11, paragraph [0081]). (i) Antibodies e.g., polyclonal or monoclonal antibodies) may be conjugated to ephrin-B2 (page 12, paragraph [0085]. (j) The extracellular domain of the ephrin family

ligand or the extracellular domain of an Eph family receptor is fused to the Fc domain of human immunoglobin (page 12, paragraph [0086]; page 17, Example 13). Anderson et al fail to disclose a kit comprising the ephrin-B2 compositions and specifically state that the composition may for vascular cell death.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Anderson et al and use the ephrin-B2 composition for imaging tumors, causing vascular cell death, delivering an agent to the vasculature, and generating a kit comprising the ephrin-B2 composition because: (1) Anderson et al disclose imaging tumors and delivering an agent to the vasculature (see discussion above). In addition, it would be obvious to use the composition for causing vascular cell death because a skilled practitioner in the art would recognize that if you inhibit tumor growth by administering an ephrin-B2 composition, then cell death is occurring since the tumor's growth is inhibited. In regards to generating a kit comprising the composition components, it would be obvious to one of ordinary skill in the art at the time the invention was made to generate a kit for diagnostic and therapeutic purposes because of the ever present need for such kits in hospitals, clinics, or other medical facilities. In addition, a skilled artisan would be capable of putting the various components of the composition in packages to be later mixed and used in such facilities.

Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate the ephrin B2 molecule a radionuclide or chelate and use various methods of detecting the accumulated composition because in

various sections of Anderson et al, it is disclosed that a labeled ligand or a labeled ligand plus a test compound may be conjugated to the ephrin B2 molecule. The label may be a radioactive isotope or a fluorescent label (page 6, paragraph [0045]; page 9, paragraph [0068]; page 11, paragraph [0079]; and page 10, paragraph [0077]). Furthermore, a skilled practitioner in the art would recognize that depending upon the agent (e.g., label) attached to the composition, the means of detecting that label would vary (i.e., NMR, x-ray, SPECT, etc).

CLAIM OBJECTIONS

7. Claims 47, 48, 50, 51, 60, 61, 63, and 64 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 47, 48, 50, 51, 60, 61, 63 and 64 are allowable over the prior art of record because the prior art neither anticipates nor renders obvious the limitations of the dependent claims in combination with all of their respective intervening claims. The claims are distinguished over the prior art because the art neither anticipates or renders obvious methods of causing cell death or uses thereof wherein an ephrin-B2 nucleic acid or polypeptide is coupled to gelonin, ricin A, ricin B, saporin, bryodin 1, bryodin 2, momordin, pokeweed antiviral protein from seeds, trichokirin, abrin, carboplatin, cisplatin, vincristine, methotrexate, paciltaxel, docetaxel, 5-fluorouracil, UFT, hydroxyurea, gemcitabine, vinorelbine, irinotecan, tirapazamine, or matrilysin.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Mon.-Fri. (alternate Mon.), 6:45 a.m. - 4:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (703) 308 - 2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

D. L. Jones
Primary Examiner
Art Unit 1616

September 2, 2003